PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-289WO	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB 02/05590	International filing date *(day/month/year)* 23.12.2002	Priority date *(day/month/year)* 23.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D207/14		
Applicant RANBAXY LABORATORIES LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 22.07.2004	Date of completion of this report 02.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Seitner, I Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/05590

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4-7 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 4-7 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-3,8-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4-7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

IV.1. According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".

This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

IV.2. For the purpose of unity, a single general inventive concept is required.
It is considered that the problem to be solved by the present application is the provision of further compounds for the treatment of respiratory, urinary, and gastrointestinal disorders.
The solution is provided by pyrrolidine derivatives according to formula (I) of claim 1.
Thus, the single general concept can be identified as the provision of pyrrolidine derivatives according to the formula (I) of claim 1 for the treatment of respiratory, urinary, and gastrointestinal disorders.

IV.3. The following documents were retrieved during the preliminary search:

D1: US-A-3 091 570 (BIEL JOHN H) 28 May 1963 (1963-05-28)

D1 discloses (see example 2, col. 2, lines 32-38, col. 3, lines 12-32) a compound of present formula (I) of claim 1 in X=O, R1=OH, Z-W-R=ethyl, n=1, R2=R3=R4=R5=R6=H for the treatment of gastrointestinal disorders such as peptic ulcer, ulcerative colitis, irritable bowel.

The compound of D1 solves the problem, namely the provision of further compounds for the treatment of gastrointestinal disorders in an identical manner to the present application. Thus, D1 provides a solution to the problem identified in the above mentioned single general concept. Therefore, the single general concept which could link the different inventions of the present application cannot be considered as inventive and there is a lack of unity.

IV.4. In the light of the above, the following four inventions have been identified:

1.) Compounds according to formula (I) of claim 1 in which X represents oxo as well as their pharmaceutical use and compositions and the process for making them.

2.) Compounds according to formula (I) of claim 1 in which X represents amino as well as their pharmaceutical use and compositions and the process for making them.

3.) Compounds according to formula (I) of claim 1 in which X represents lower alkyl(C_1-C_4)amino as well as their pharmaceutical use and compositions and the process for making them.

4.) Compounds according to formula (I) of claim 1 in which X represents lower alkoxy(C_1-C_4) as well as their pharmaceutical use and compositions and the process for making them.

IV.5. This Authority chose not to invite the Applicant to restrict the application or to pay additional fees and consequently, all part of the present application are subject to the following examination.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US-A-3 091 570 (BIEL JOHN H) 28 May 1963 (1963-05-28)
D2: US-A-2 956 062 (LUNSFORD CARL D) 11 October 1960 (1960-10-11)
D3: BERNARD V. FRANKO ET AL: "Derivatives of 3-Pyrrolidinols-III. The Chemistry, Pharmacology, and Toxicologyof some N-Substituted-3-Pyrrolidyl alpha-Substituted Phenylacetates" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, vol. 2, 1960, pages 523-529, XP008021298
D4: BIEL J H ET AL: "CENTRAL STIMULANTS. II. CHOLINERGIC BLOCKING AGENTS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 26, 1961, pages 4096-4103, XP002067288 ISSN: 0022-3263
D5: EP-A-0 012 071 (SYNTEX INC) 11 June 1980 (1980-06-11)
D6: EGLEN R M ET AL: "MUSCARINIC RECEPTOR LIGANDS AND THEIR THERAPEUTIC POTENTIAL" CURRENT OPINION IN CHEMICAL BIOLOGY, CURRENT BIOLOGY LTD, LONDON, GB, vol. 3, no. 4, August 1999 (1999-08), pages 426-432, XP000972296 ISSN: 1367-5931
D7: EP-A-0 388 054 (PFIZER LTD ;PFIZER (US)) 19 September 1990 (1990-09-19)
D8: WO 98/21183 A (NOE CHRISTIAN R ;WAELBROECK MAGALI (BE); LAMBRECHT GUENTER (DE); C) 22 May 1998 (1998-05-22)
D9: EP-A-0 823 423 (BANYU PHARMA CO LTD) 11 February 1998 (1998-02-11)
D10: WO 02/04402 A (BANYU PHARMA CO LTD ;MATSUDA KENJI (JP); KURIHARA HIDEKI (JP); OGI) 17 January 2002 (2002-01-17)
D11: YUFU SAGARA ET AL: "Cyclohexylmethylpiperidinyltriphenylpropi onamide: a selective muscarinic M3 antagonist discriminating against the other receptor subtypes" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, no. 4, 2002, pages 984-987, XP002238502 ISSN: 0022-2623
D12: US-B-6 174 9001 (TAKAHASHI YOSHINORI ET AL) 16 January 2001 (2001-01-16)
D13: EP-A-0 863 141 (BANYU PHARMA CO LTD) 9 September 1998 (1998-09-09)

D14: EP-A-0 930 298 (BANYU PHARMA CO LTD) 21 July 1999 (1999-07-21)

D15: TANIGUCHI K ET AL: "AGENTS FOR THE TREATMENT OF OVERACTIVE DETRUSOR. VI. SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF ACETAMIDE DERIVATIVES BEARING CYCLIC AMINES IN N-SUBSTITUENTS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 42, no. 1, 1994, pages 74-84, XP002067286 ISSN: 0009-2363

D16: O'NEILL, JOHN J. ET AL: "Biochemical effects of psychotomimetic anticholinergic drugs" ADVANCES IN BIOCHEMICAL PSYCHOPHARMACOLOGY (1972), 6, 203-18, XP008026629

V.1. Novelty:

Documents D1-D4 and D16 discloses compounds which fall within the scope of the general formula I of present claim 1 and which are useful for the treatment of gastrointestinal disorders such as peptic ulcer, ulcerative colitis, irritable bowel (see in D1: example 2, col. 2, lines 32-38, col. 3, lines 12-32), inhibitors of gastrointestinal motility (see in D2 table I, col. 2, lines 3-8), (see in D3: examples 504, 379, 371, 372, 480, 479, 484, 487, 485, table I, pages 534-538), or cholinergic blocking agents (see in D4: examples 1, 3: table II, examples 11, 13, table III), (see in D16 pages 203-204).

Document D5 discloses intermediates (see page 10, lines 32-35) which are covered by the present formula I of claim 1.

Consequently, the **subject-matter of claim 1-17 is not novel over the prior art (Article 33(2) PCT).**

V.2. Inventive Step:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-17, in as far as novel, does not involve an inventive step in the sense of Article 33(3) PCT:

V.2.1. With respect to invention 1 in which X represents oxo, the document D9 which is regarded as being the closest prior art, discloses (example 20, table 1, claims 1, 10, 11) muscarinic receptor antagonists from which the subject-matter of claim 1 differs in that a

pyrrolidine ring is bound to the -C(=O)-O- group, whereas in D9 it is a piperidine ring.

The problem to be solved by the present invention may therefore be regarded as the provision of further compound as muscarinic receptor antagonists for the treatment of respiratory, urinary, or gastrointestinal disorders.

However, documents D8 (see examples 1,2, claims 1,17,18) and D10 (see examples 16-22, 27-30,40) disclose muscarinic antagonists and/or compounds for the treatment of asthma and gastrointestinal disorders comprising such a pyrrolidine ring linked to the -C(=O)-O- group.

Therefore, it would have been obvious to the skilled person to combine the teaching of D9 with the features of D8 and D10 in order to provide further compounds as muscarinic receptor antagonists for the treatment of respiratory, urinary, or gastrointestinal disorders.

V.2.2. With respect to invention 2 in which X represents amino, the document D9, D11, D12, D13, and D14 which are regarded as being the closest prior art, disclose (see International Search Report for details on citations) muscarinic receptor antagonists from which the subject-matter of claim 1 differs in that a pyrrolidine ring is bound to the amide group, whereas in D9, D11, D12, D13, and D14 it is a piperidine ring.

However, documents D6 and D7 disclose muscarinic receptor antagonists comprising a pyrrolidine ring and therefore the skilled person would have been lead to incorporating a pyrrolidine ring in the compounds known from D9, D11, D12, D13, and D14.

V.2.3. With respect to invention 3 in which X represents lower alkyl(C_1-C_4)amino, the document D15 which is regarded as being the closest prior art, discloses (see example 4c-4g, col.1) compounds for the treatment of urinary disorders from which the subject-matter of claim 1 differs in that a cycloalkyl ring is bound to the Ph-C(R1)- group, whereas in D15 it is a phenyl ring.

However, this (cycloalkyl)(Ph)-C(R1)- group is known for example from D9-D15 and it would have therefore been obvious to the skilled person to replace a phenyl ring by a cycloalkyl ring.

V.2.4. With respect to invention 4 in which X represents lower alkoxy(C_1-C_4), the document D10 which is regarded as being the closest prior art, discloses (see examples 23,24, 27-30) muscarinic receptor antagonists from which the subject-matter of claim 1 differs in that a cycloalkyl ring is not substituted by fluorine, whereas in the general formula (I) D10, R1 represents a fluorine-substituted C_4-C_6 cycloalkyl.

However, muscarinic antagonists with unsubstituted cycloalkyl rings are known for example from D9, D12, D13, D14. From this teaching, the skilled person would have been lead to use cycloalkyl rings which are not substituted by fluor.

Consequently, the **subject-matter of claims 1-17** of the present application **cannot be considered as involving an inventive step (Article 33(3) PCT).**

V.3. Industrial Applicability:
The present application relates to compounds which are useful for the treatment of respiratory, urinary, or gastrointestinal disorders and the **subject-matter of claims 1-3, 8-17** is therefore **industrially applicable (Article 33(4) PCT).**

For the assessment of the present claims 4-7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.